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Systematic Reviews and Meta- and Pooled Analyses

A Pooled Analysis of Extremely Low-Frequency Magnetic Fields and Childhood Brain Tumors

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Pooled analyses may provide etiologic insight about associations between exposure and disease. In contrast to childhood leukemia, no pooled analyses of childhood brain tumors and exposure to extremely low-frequency magnetic fields (ELF-MFs) have been conducted. The authors carried out a pooled analysis based on primary data (1960–2001) from 10 studies of ELF-MF exposure and childhood brain tumors to assess whether the combined results, adjusted for potential confounding, indicated an association. The odds ratios for childhood brain tumors in ELF-MF exposure categories of 0.1–<0.2 μT, 0.2–<0.4 μT, and ≥0.4 μT were 0.95 (95% confidence interval: 0.65, 1.41), 0.70 (95% CI: 0.40, 1.22), and 1.14 (95% CI: 0.61, 2.13), respectively, in comparison with exposure of <0.1 μT. Other analyses employing alternate cutpoints, further adjustment for confounders, exclusion of particular studies, stratification by type of measurement or type of residence, and a nonparametric estimate of the exposure-response relation did not reveal consistent evidence of increased childhood brain tumor risk associated with ELF-MF exposure. These results provide little evidence for an association between ELF-MF exposure and childhood brain tumors.

brain neoplasms; child; electromagnetic fields; meta-analysis

Abbreviations: CI, confidence interval; ELF-MF, extremely low-frequency magnetic field; OR, odds ratio; UKCCS, United Kingdom Childhood Cancer Study.

Since 1979, numerous residential studies have examined the potential association between exposure to extremely low-frequency magnetic fields (ELF-MFs) and childhood cancer (1, 2). The initial research examined all childhood cancers as an endpoint, but later focus shifted to a potential association between residential ELF-MF exposure and childhood leukemia (3). Two pooled analyses (4, 5) have provided a basis for concluding that an association exists between residential exposure to ELF-MFs above 0.3 μT/0.4 μT and the risk of childhood leukemia. Based largely on this epidemiologic association, the International Agency for Research on Cancer has classified ELF-MF exposure as possibly carcinogenic to humans (Group 2B) (6).

Evidence linking childhood brain tumors to residential ELF-MF exposure appears to be weaker. Individual studies of childhood brain tumors, usually suffering from even smaller numbers of exposed cases than leukemia studies, have generally been unable to examine the potential association with elevated ELF-MF exposure with satisfactory statistical precision. In a recent meta-analysis, Mezei et al. (7) found no overall increase in childhood brain tumor risk, with the exception of high-cutpoint analyses (0.3 μT or 0.4 μT), where the possibility of a moderate risk increase could not be excluded. Unlike studies of childhood leukemia, however, to our knowledge no pooled analyses of brain tumors and ELF-MFs have been conducted. Such an analysis was identified as a high research priority in the World Health Organization research agenda issued in 2007 (8).

We carried out a pooled analysis based on primary data from 10 studies of ELF-MFs and childhood brain tumors to assess whether the combined results, adjusted for potential confounding, indicated an association between ELF-MF exposure and childhood brain tumors.

MATERIALS AND METHODS

We searched the published literature through PubMed, as well as references of identified papers, and conducted an informal survey of epidemiologists involved in ELF-MF research to identify relevant studies on residential ELF-MF exposure and childhood brain tumors. To be included, studies had to provide data for children, provide separate data for cancers of the brain or central nervous system, and provide measured or calculated values for residential exposure to ELF-MFs.

We identified 16 studies published between 1979 and 2010, of which 10 could be included in the pooled analyses (Table 1). Four studies (2, 9–11) were not included because they did not have measurements or calculated fields for childhood brain tumors. One study (12) was not included because it used dwellings rather than persons as units of analysis, included only outside spot measurements, and overlapped with another study (13). A sixth study (14) was not included because its cases were a small subset of those from another study (15). Appendix Table 1 summarizes the methods and findings of the studies that did not meet our inclusion criteria. Two included studies had a large overlap, with perhaps 90% of the cases in the United Kingdom Childhood Cancer Study (UKCCS) (16) also being included in the Kroll et al. (15) study, but they differed in terms of type of exposure surrogates and timing of exposure. To maintain independence of observations, we included only 1 of these studies in any given analysis. Investigators in the UKCCS (16) used a 2-phase measurement strategy, in which 48-hour measurements were conducted when either a shorter measurement (108 minutes) or a characteristic of the residence indicated that ELF-MF exposure was elevated. In this pooled analysis, we used only second-phase measurements, which were taken for all subjects (with their matched cases or controls) who had potential sources of high exposure (>0.1 μT) in the first phase.

Investigators utilized stratified sampling of controls in all of the studies, although the stratification variables were not the same in all studies. In Finland, the authors of the original publication reported findings from a cohort study (17), but in preparation for this pooled analysis, a control group was selected and the data were evaluated using a matched case-control design with 6 additional years of follow-up. For some studies, the same controls were used for both brain tumors and leukemia cases in the original publications, and we maintained the same approach in these instances. Since we wanted to use as many of the cases and controls as possible to increase the flexibility of the analysis, we ignored the matching and instead included adjustment for age at diagnosis, gender, and study.

To make the data as consistent as possible across studies, we limited the age of diagnosis to 0–15 years inclusive and converted all measurements to microteslas. One Finnish patient with 3 tumors was included only once. One Japanese patient with cavernous angioma and 2 corresponding controls were excluded. However, germ-cell tumors and corresponding controls were included in the analysis, although these tumors were not consistently included in all individual studies.

We focused on ELF-MFs present in the general area of the home; that is, we excluded exposure occurring in schools, data on which would have been available for only 1 study (UKCCS) (16), and did not include short-duration exposures close to appliances. In all studies, investigators took long-term measurements or spot measurements and/or calculated the strengths of ELF-MFs. Only 2 of the included studies, both from the United States (18, 19), had information on wire codes, but they also had measurements. We did not use wire codes in the analyses. With regard to long-term measurements, measurements were taken for 24 hours in 2 studies (18, 20), for 48 hours (for highly exposed subjects) in 1 study (16), and for a 1-week period in 1 study (21); these measurements are referred to as "long-term measurements" throughout this paper. Arithmetic mean values rather than geometric means were used, since these were available for all studies.

Our analyses included separate analyses for long-term measurements, calculated fields, and spot measurements. Investigators had collected data from the child's birth home, the home in which the child had lived longest prior to diagnosis, the latest home in which the child had lived prior to diagnosis that was near a power line, and/or the home in which the child was living at diagnosis. For subjects with data from more than 1 home, we used the following hierarchy to select a single exposure proxy for the analysis: Diagnosis home was used if data were available; if not, then the latest home lived in before diagnosis; if not, then the home lived in the longest; and if not, then birth home. We also performed separate analyses for diagnosis homes, longest-lived-in homes, and birth homes. For these analyses, for subjects with more than 1 type of exposure proxy, we used long-term measurements if they were available; if not, then we used calculated fields; and if neither measure was available, then we used spot measurements. In addition, in an attempt to maximize the available sample size, we conducted a "best measure" pooled analysis in which we selected a single best exposure measurement for each subject using both the exposure metric hierarchy (long-term over calculated fields over spot) and the home hierarchy (diagnosis over latest over longest-lived-in over birth). The choice between selection of type of exposure metric before residence and selection of residence before type of exposure metric was immaterial, since both approaches yielded identical measurements for each subject.

Additional potential confounders for which data were available included type of dwelling, mobility, urbanization, socioeconomic status, and exposure to traffic exhaust. The number, type, and coding of potential confounders differed among the studies (see Table 1). We examined socioeconomic status (standardized to a 3-level ordinal variable), urbanization (dichotomized as urban/rural), dwelling type (dichotomized as single-family/multiple-unit), and mobility (dichotomized as number of residences before diagnosis: 1/>1).

Table 1. Characteristics of Studies Included in a Pooled Analysis of Childhood Brain Tumors and Extremely Low-Frequency Magnetic Field Exposure, 1960–2001

First Author, Year (Reference No.)	Country	Subjects			Exposure Measure			Potential Confounders[a]					Participation Rate, %		Type(s) of Home Exposure Measured
		No. of Cases[b]	No. of Controls[b]	Years of Diagnosis	Long-Term Measurements	Spot Measurements	Calculated Fields	Dwelling Type (Single-Family vs. Multiple-Unit)	Mobility	SES	Urbanization	Exposure to Traffic Exhaust	Cases	Controls	
Feychting, 1993 (13)	Sweden	33	549	1960–1985		√	√	√	√	√	√		N/A	N/A	Birth, longest, latest, diagnosis[d]
Kroll (15)	United Kingdom	6,593	6,584	1962–1995			√			√	√		N/A	N/A	Birth
UKCCS, 1999 (16)	United Kingdom	602	611	1991–1994	√	√	√		√	√	√		88[g]	88[g]	Diagnosis
Verkasalo, 1993 (17)	Finland	39	391	1974–1996			√		√				N/A	N/A	Birth, longest, latest, diagnosis
Preston-Martin, 1996 (18)	United States	183	139	1984–1992	√	√		√	√	√			59[h]	54[h]	Diagnosis
Savitz, 1988 (19)	United States	24	198	1976–1983		√				√			38	59	Diagnosis
Schuz, 2001 (20)	Germany	64	414	1988–1994	√	√		√	√	√	√	√	63	66	Longest
Saito, 2010 (21)	Japan	54	97	1999–2001	√	√			√	√	√		76[e]	52	Diagnosis
Olsen, 1993 (25)	Denmark	624	1,872	1968–1986			√	√	√	√	√		N/A[c]	N/A	Birth, diagnosis[d]
Tynes, 1997 (26)	Norway	156	639	1965–1989			√	√	√	√			N/A	N/A	Latest[f]

Abbreviations: N/A, not applicable; SES, socioeconomic status; UKCCS, United Kingdom Childhood Cancer Study.
[a] Year of birth and gender were available for all studies.
[b] Numbers of cases and controls presented in the table are for subjects with available measurements.
[c] N/A because the study did not involve participation.
[d] Fields were calculated for birth home and for the entire period.
[e] Case participation; additionally, only 43% of physicians agreed to participate.
[f] Fields were calculated for the entire period.
[g] For calculated fields; 66% for measured fields.
[h] For electromagnetic field measurements, overall study participation rates were higher.

Table 2. Distribution of Childhood Brain Tumor Cases and Controls by Extremely Low-Frequency Magnetic Field Exposure Metric, Study, and Exposure Level, 1960–2001

Exposure Metric and Study (Reference No.)	Extremely Low-Frequency Magnetic Field Exposure, μT										Total	
	<0.1		0.1–<0.2		0.2–<0.3		0.3–<0.4		≥0.4			
	No. of Cases	No. of Controls	No. of Cases	No. of Controls	No. of Cases	No. of Controls	No. of Cases	No. of Controls	No. of Cases	No. of Controls	No. of Cases	No. of Controls
Long-term measurement												
UKCCS, 1999 (16)	63	65	12	9	1	1	1	0	0	1	77	76
Preston-Martin, 1996 (18)	66	56	12	10	4	6	3	1	6	5	91	78
Schuz, 2001 (20)	56	372	6	29	1	7	0	4	1	2	64	414
Saito, 2010 (21)	47	84	3	8	0	4	2	0	2	1	54	97
Total	232	577	33	56	6	18	6	5	9	9	286	665
Calculated fields												
Feychting, 1993 (13)	29	471	2	33	0	14	0	9	2	22	33	549
Kroll (15)	6,589	6,577	2	4	0	0	1	0	1	3	6,593	6,584
Verkasalo, 1993 (17)	34	363	4	17	0	6	0	3	1	2	39	391
Olsen, 1993 (25)	621	1,863	1	1	0	3	0	4	2	1	624	1,872
Tynes, 1997 (26)	149	606	2	14	2	6	1	2	2	11	156	639
Total	7,422	9,880	11	69	2	29	2	18	8	39	7,445	10,035
Spot measurement												
Feychting, 1993 (13)	10	205	8	67	3	28	0	9	2	32	23	341
UKCCS, 1999 (16)	62	66	11	6	3	2	1	0	0	3	77	77
Preston-Martin, 1996 (18)	140	93	17	22	7	4	1	2	3	2	168	123
Savitz, 1988 (19)	18	155	4	28	1	10	1	3	0	2	24	198
Schuz, 2001 (20)	55	351	8	47	1	8	0	2	0	6	64	414
Saito, 2010 (21)	41	84	4	2	1	3	2	2	1	0	49	91
Total	326	954	52	172	16	55	5	18	6	45	405	1,244
Best measurement												
Feychting, 1993 (13)	29	471	2	33	0	14	0	9	2	22	33	549
Kroll (15)	6,589	6,577	2	4	0	0	1	0	1	3	6,593	6,584
UKCCS, 1999 (16)	588	598	12	10	1	1	1	0	0	2	602	611
Verkasalo, 1993 (17)	34	363	4	17	0	6	0	3	1	2	39	391
Preston-Martin, 1996 (18)	144	100	22	21	6	8	4	3	7	7	183	139
Savitz, 1988 (19)	18	155	4	28	1	10	1	3	0	2	24	198
Schuz, 2001 (20)	56	372	6	29	1	7	0	4	1	2	64	414
Saito, 2010 (21)	47	84	3	8	0	4	2	0	2	1	54	97
Olsen, 1993 (25)	621	1,863	1	1	0	3	0	4	2	1	624	1,872
Tynes, 1997 (26)	149	606	2	14	2	6	1	2	2	11	156	639
Total	8,275	11,189	58	165	11	59	10	28	18	53	8,372	11,494

Abbreviation: UKCCS, United Kingdom Childhood Cancer Study.

Statistical methods

An analysis plan that included hypotheses, hierarchy of measurements, and cutpoints was developed and agreed upon prior to analysis. The data were analyzed using both ordinary logistic regression, with fixed intercepts to adjust for study, and mixed-effects logistic regression, with random intercepts and exposure effect coefficients for study. Separate intercepts were used for East Germany and West Germany. Ordinary and mixed-effects logistic regression gave similar results; we present results for ordinary logistic regression.

We conducted an analysis using best measures with continuous exposure as a linear predictor, reporting results as the odds ratio for an increase of 0.2 μT. We also used this analysis for a likelihood ratio test of homogeneity of effects across studies, in which models with and without study-specific coefficients for exposure were compared. In addition, we estimated the trend in the log odds of being a case using a generalized additive model (22), using a nonparametric curve (natural cubic smoothing spline with interior and boundary knots at the unique values of exposure) to estimate the risk associated with exposure, while controlling

Table 3. Odds Ratios for Childhood Brain Tumors According to Extremely Low-Frequency Magnetic Field Exposure, by Exposure Metric and by Type of Residence, 1960–2001[a]

Exposure Metric	Studies Included (Reference Nos.)	Extremely Low-Frequency Magnetic Field Exposure, μT					
		0.1–<0.2		0.2–<0.4		≥0.4	
		OR	95% CI	OR	95% CI	OR	95% CI
Type of measurement							
Long-term	16, 18, 20, 21	1.13	0.69, 1.87	0.94	0.43, 2.06	1.35	0.39, 3.71
Calculated fields	13, 15, 17, 25, 26	1.06	0.53, 2.11	0.56	0.19, 1.60	1.21	0.53, 2.78
Spot	13, 16, 18–21	1.16	0.79, 1.72	1.21	0.67, 2.18	0.68	0.26, 1.80
Type of home exposure[b]							
Home at diagnosis	13, 16–21, 25, 26	0.89	0.60, 1.31	0.77	0.44, 1.36	1.08	0.54, 2.16
Longest-lived-in home	13, 16, 17, 20	1.42	0.79, 2.56	0.86	0.28, 2.65	2.19	0.57, 8.44
Birth home	13, 15, 17, 20, 25, 26	1.03	0.59, 1.80	0.79	0.34, 1.80	1.14	0.52, 2.49

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Reference group: <0.1 μT. All results were obtained using ordinary logistic regression with intercepts for study and adjustment for age at diagnosis and gender.

[b] Hierarchy of choice of exposure metric: long-term measurements, then calculated fields, and then spot measurements.

for study, age, and gender. The amount of smoothing is determined by the degrees of freedom (df), with higher df corresponding to less smoothing. For this analysis, we transformed exposures using an inverse cubic transformation to reduce the influence of outliers at high exposure levels. These analyses were conducted using the gam package in R, version 2.9.2 (23).

In other analyses, we used increasing exposure categories of 0.1–<0.2 μT, 0.2–<0.4 μT, and ≥0.4 μT to examine the exposure-response relation, with a reference category of <0.1 μT. Single cutpoints at 0.3 μT and 0.4 μT were also explored. We also obtained odds ratios using a moving window of exposure. These analyses used exposure categories of 0.1–<0.2 μT, 0.15–<0.25 μT, 0.20–<0.30 μT, 0.25–<0.35 μT, ≥0.30 μT, ≥0.35 μT, and ≥0.40 μT, with a reference category of <0.1 μT, and results were adjusted for age, gender, and study. Treating age at diagnosis as continuous or categorical gave similar results; results obtained with age included as a continuous variable are presented. The influence of individual studies was examined by omitting 1 study at a time. These analyses were conducted using Stata 10 (24).

RESULTS

Among the included studies, 7 were conducted in Europe (13, 15–17, 20, 25, 26), 2 in the United States (18, 19), and 1 in Japan (21). In 4 studies (16, 18, 20, 21), investigators examined childhood brain tumor risk in relation to long-term exposure to ELF-MFs, and in 5 studies (13, 15, 17, 25, 26) they used calculated ELF-MFs. Spot ELF-MF measurements were available in 6 studies (13, 16, 18–21); spot measurements were the only available exposure metric in 1 study (19) (Table 1).

Table 1 also shows the numbers of cases and controls for each study, along with data on variables supplied in those publications. There were a total of 8,372 cases and 11,494 controls with 1 or more of the 3 types of exposure metrics, and 79% of cases were contributed by the large registry-based United Kingdom case-control study (15). However, numbers in the high-exposure categories remained small even for this large set of data.

Table 2 shows the distribution of subjects by exposure level for long-term, spot, and calculated field studies. The number of subjects with values below 0.3 μT varied by study. Values above 0.3 μT or 0.4 μT were relatively infrequent in all studies, even in studies that focused on the population living next to power lines (ranging from 0.03% to 6.53% for fields above 0.4 μT).

Table 3 presents results by type of exposure metric. The pattern was not consistent: Risk did not increase with increasing exposure. Notable features were dips in the odds ratios for 0.2–<0.4 μT versus <0.1 μT for calculated fields and ≥0.4 μT versus <0.1 μT for spot measurements.

Table 3 also presents results by residence for which the estimate of exposure was obtained. These analyses included calculated fields for some studies and long-term measurements for others; the analysis for home at diagnosis included all 3 types of measurements. The highest odds ratio for ≥0.4 μT versus <0.1 μT was for the longest-lived-in home; however, this was based on only 3 exposed cases. Again, there was no clear exposure-response pattern.

The continuous best-measure exposure analysis gave an odds ratio estimate of 0.96 for each 0.2-μT increase in exposure (95% confidence interval (CI): 0.86, 1.07). The homogeneity test based on this analysis yielded a χ^2 statistic (8 df) of 5.78, corresponding to a P value of 0.672, which supports the appropriateness of pooling.

Table 4 presents results from the best-measure analysis with categorical exposure levels, along with adjustment for a number of potential confounders. Because the 2 United Kingdom studies (15, 16) included a large overlap of subjects, we present results with only 1 of those studies included in any given analysis. Not all potential confounders were available in all studies. Analyses adjusting for

Table 4. Odds Ratios for Childhood Brain Tumors According to Extremely Low-Frequency Magnetic Field Exposure, Based on the Best Available Measure, With Adjustment for Potential Confounders and Subgroups, 1960–2001[a]

Adjustment Factor(s)	Studies Included (Reference Nos.)	Extremely Low-Frequency Magnetic Field Exposure, μT					
		0.1–<0.2		0.2–<0.4		≥0.4	
		OR	95% CI	OR	95% CI	OR	95% CI
Adjustment for age and gender	13, 15, 17–21, 25, 26						
Study		0.95	0.64, 1.40	0.69	0.40, 1.22	1.14	0.61, 2.14
Study, age, and gender		0.95	0.65, 1.41	0.70	0.40, 1.22	1.14	0.61, 2.13
Adjustment for age and gender	13, 16–21, 25, 26						
Study		1.03	0.72, 1.47	0.71	0.41, 1.23	1.16	0.61, 2.20
Study, age, and gender		1.03	0.72, 1.48	0.71	0.41, 1.24	1.16	0.61, 2.20
Adjustment for SES after adjustment for age and gender	13, 15, 18–21, 25, 26						
Study, age, and gender		0.90	0.60, 1.37	0.76	0.43, 1.36	1.15	0.60, 2.22
Study, age, gender, and SES		0.90	0.60, 1.37	0.77	0.43, 1.37	1.15	0.60, 2.21
Adjustment for dwelling type after adjustment for age and gender	13, 18, 20, 26						
Study, age, and gender		0.83	0.50, 1.37	0.66	0.33, 1.34	0.88	0.41, 1.92
Study, age, gender, and dwelling type		0.85	0.51, 1.40	0.67	0.33, 1.36	0.90	0.41, 1.95
Adjustment for mobility after adjustment for age and gender	13, 17, 18, 20, 21, 25, 26						
Study, age, and gender		0.96	0.63, 1.48	0.61	0.33, 1.13	1.34	0.70, 2.56
Study, age, gender, and mobility		0.96	0.63, 1.48	0.61	0.33, 1.13	1.33	0.69, 2.56
Adjustment for urbanization after adjustment for age and gender	13, 15, 21, 25						
Study, age, and gender		1.00	0.53, 1.89	0.52	0.17, 1.56	1.84	0.74, 4.59
Study, age, gender, and urbanization		1.00	0.53, 1.89	0.52	0.17, 1.56	1.85	0.74, 4.61
Subgroup with single residence before diagnosis	13, 16–18, 20, 21, 25, 26						
Study, age, and gender		0.63	0.33, 1.21	0.89	0.39, 2.00	1.34	0.56, 3.23
Age subgroups, adjusted for study, age, and gender	13, 15, 17–21, 25, 26						
Age at diagnosis <8 years		1.11	0.66, 1.89	0.92	0.46, 1.81	0.95	0.42, 2.13
Age at diagnosis ≥8 years		0.77	0.43, 1.38	0.43	0.14, 1.28	1.49	0.55, 3.98

Abbreviations: CI, confidence interval; OR, odds ratio; SES, socioeconomic status.
[a] Reference group: <0.1 μT. All results were obtained using ordinary logistic regression with intercepts for study.

confounding were carried out in the subset of studies and subjects for whom data on the confounder were available. While risks for a given subset varied, adjustment did not change the odds ratio estimates. All confidence intervals included the null value. Results shown here and elsewhere were similar when a cutpoint of 0.3 μT was used (data not shown).

Examination of the residentially stable subgroup also did not show an increase in risk with exposure (Table 4). We evaluated age as a possible effect modifier by stratifying the sample at age 8 years at diagnosis (bottom of Table 4). While the odds ratio for the ≥0.4-μT category was higher in the older age group, the odds ratios for the lower exposure categories were lower in the older age group, and the results did not provide consistent evidence that the effect of exposure varied by age.

Odds ratio estimates using categorical cutpoints and involving relatively small numbers of subjects are vulnerable to unstable results. To address this concern, we also calculated odds ratios using a moving window of exposure levels (Figure 1). These results did not suggest a trend of increasing risk with increasing exposure: There was a dip in the intermediate exposure category, after which the risk returned to 1.

Figure 2 presents nonparametric estimates of the trend in the log odds of being a case from a generalized additive model, with adjustment for study, age, and gender. The confidence intervals widen as exposure increases, reflecting the smaller number of subjects at high exposure levels. The curves suggest only variation around the null value of zero. The spikes are artifacts created when multiple subjects have coinciding case/control status and exposure values.

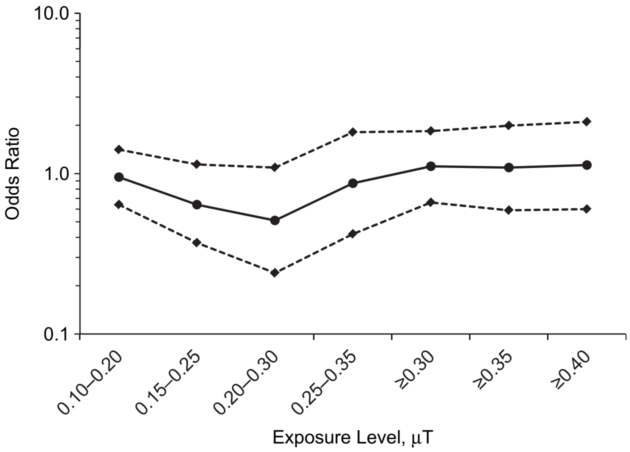

Figure 1. Odds ratios (solid line) and 95% confidence intervals (dashed lines) for childhood brain tumors in a moving window of extremely low-frequency magnetic field exposure levels, adjusted for age at diagnosis, gender, and study, 1960–2001. Reference category: <0.1 μT.

Influence analyses omitting studies one at a time yielded odds ratios for ≥0.4 μT versus <0.1 μT ranging from 0.99 to 1.41, with adjustment for gender and age at diagnosis. Omission of any individual study from the analysis did not produce important changes in the summary odds ratio (Figure 3). The most influential study was the study by Preston-Martin et al. (18). Although this study was relatively small in terms of the overall number of subjects, it had the highest number of exposed cases (7 cases with exposure of ≥0.4 μT); the other studies had 0–2 cases in this exposure category. The odds ratio for the 4 methodologically similar Nordic studies (13, 17, 25, 26) (combined odds ratio (OR) = 1.53, 95% CI: 0.65, 3.59), which were record-based and thus thought to be less susceptible to selection bias, was higher than the odds ratio for the other studies (15, 16, 18–21) (combined OR = 0.78, 95% CI: 0.36, 1.70).

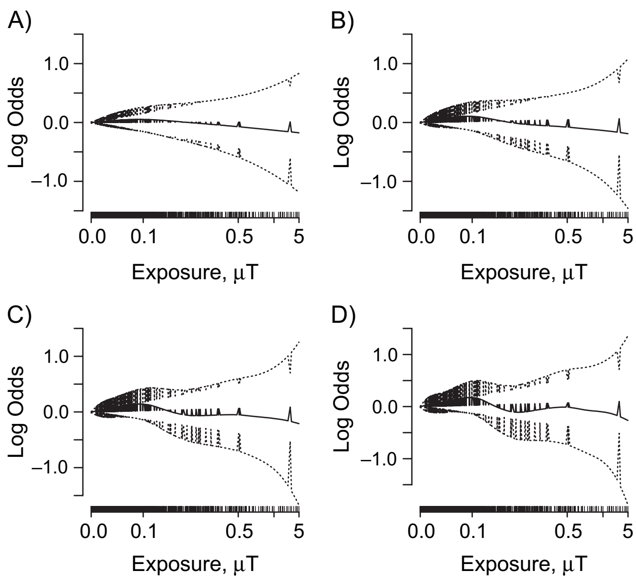

Figure 2. Nonparametric estimates of trend in the log odds of childhood brain tumors according to extremely low-frequency magnetic field exposure, with a range of smoothing levels from a generalized additive model using a natural cubic smoothing spline for exposure, 1960–2001. Results were adjusted for age at diagnosis, gender, and study. Rug plots at the bottom of each panel indicate the exposure values of subjects included in the analysis. Panel A, 2 df; panel B, 3 df; panel C, 4 df; panel D, 5 df. Dashed lines, 95% confidence interval.

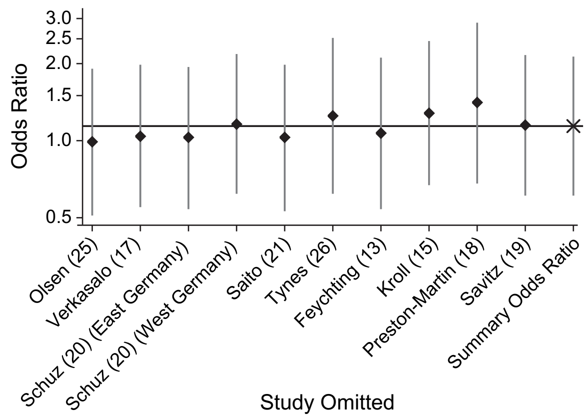

Figure 3. Influence analysis of the summary odds ratio for childhood brain tumors according to extremely low-frequency magnetic field exposure of ≥0.4 μT versus <0.1 μT, with omission of individual studies, 1960–2001. Results were adjusted for age at diagnosis, gender, and study. Bars, 95% confidence interval.

DISCUSSION

We conducted a pooled analysis of 10 epidemiologic studies on the association of residential ELF-MF exposure and childhood brain cancer. Pooled analysis, considered the gold standard for synthesizing results from multiple studies, allows for comparison across different studies and metrics, free of artifacts introduced by analytic differences, and for derivation of statistically more stable results. Pooled analysis uses raw data from previous studies and thus can apply identical analyses to all included studies. The choices of cutpoints, reference groups, metrics, etc., in a pooled analysis may differ from the choices made in the original studies and may result in changes in the study-specific effect estimates.

Results from pooled analyses, however, are prone to the same biases that might have been operating in the original studies. The studies using measurements generally had low participation rates (40%–80% as reported in the original studies) and thus had large potential for selection bias (27, 28). Studies estimating risks for calculated fields do not require participation and thus are less vulnerable to selection bias, but they neglect sources of ELF-MFs other than high-voltage power lines and thus are likely to introduce exposure misclassification and loss of statistical power. In the United Kingdom, for example, it has been shown that high-voltage sources account for only 23% of exposures above 0.2 μT and 43% of those above 0.4 μT (29). In this context, note that in order to include as many subjects as possible, we included calculated fields from the Kroll et al. (15) study in preference to the UKCCS measured fields (16) in some analyses. Since the original studies did not follow a common protocol, we were forced to make analytical choices, particularly for exposure assessment, when we combined data from individual studies. However, results were not sensitive to the choices we made and were consistent regardless of type of exposure metric used and with omission of single studies.

None of our analyses showed statistically significant increases or a consistent pattern suggestive of an association between childhood brain cancer risk and various measures of residential ELF-MF exposure. Some of the odds ratios for the highest exposure category (ELF-MFs above 0.3 μT or 0.4 μT) were elevated but had 95% confidence intervals that included 1. The pattern of odds ratios across increasing exposure categories was not consistent with an exposure-response relation; odds ratios for the middle category were mostly below 1, again with wide confidence intervals.

Our results were robust and insensitive to cutpoints, age and confounder adjustment, and various model assumptions and specification. The numbers and available information did not allow for separate analysis of different histologic types. Although there was some heterogeneity between studies, our results were not driven by any single study.

In the previous meta-analysis, results from 13 epidemiologic studies of childhood brain cancer provided no strong evidence for an increase in risk with residential exposure to ELF-MFs (7). The suggestion of a moderate risk increase at higher exposure levels (>0.3 μT or 0.4 μT), however, could not be excluded (OR = 1.68, 95% CI: 0.83, 3.43) (7).

Although our results contained hints of a risk increase in some subanalyses, as is expected when numerous analyses are performed, these increases were small, highly dependent on particular studies included in the subset, and inconsistent with regard to increasing exposure for all models chosen. Taken as a whole, our results provide little evidence for an association between ELF-MF exposure and childhood brain tumors.

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(Appendix follows)

Appendix Table 1. Characteristics and Results of Studies That Did Not Meet Criteria for Inclusion in a Pooled Analysis of Childhood Brain Tumors and Extremely Low-Frequency Magnetic Field Exposure, 1960–2001

First Author, Year (Reference No.)	Country	Study Type	Stated Disease Diagnosis	No. of Cases	No. of Controls	Dates of Diagnosis	Age, years	Exposure Measurement(s)	Results	Reason for Exclusion
Gurney, 1996 (11)	United States	Population-based case-control	Brain tumors	133	270	1984–1990	0–20	Wire code: 23 cases with high exposure	OR = 0.9, 95% CI: 0.5, 1.5	No measurements or calculated fields
Myers, 1990 (14)	United Kingdom	Case-control	Solid tumors/ nonsolid tumors	194	311	1970–1979	0–15	Calculated field distance	For ≥0.3 μT vs. <0.1 μT, OR = 3.1, 95% CI: 0.3, 31.8	Small subset of cases from the Kroll et al. (15) study
Tomenius, 1986 (12)[a]	Sweden	Case dwelling / control dwelling	All childhood tumors/nervous system tumors	294	253	1958–1973	0–18	Distance spot measurement	For spot measurement ≥0.3 μT (referent: <0.3 μT), OR = 3.7	Largely overlapped with the Feychting et al. (13) study; unit was dwelling
Dockerty, 1998 (9)	New Zealand	Population-based case-control	Leukemia, brain tumors, other solid cancers	58	58	1990–1993	0–14	Long-term 24-hour exposure to appliances	ORs for child's appliance use ranged from 0.3 to 5.5	No measurements for brain tumors
Wertheimer, 1979 (2)	United States	Proportional mortality study	Childhood tumors/ nervous system tumors	344	344	1950–1973	0–19	Wire code	% of HCC cases vs. controls: 45.5 vs. 25.8	No measurements or calculated fields
Lin, 1994 (10)	Taiwan	Hospital-based case-control	Childhood tumors/ brain cancer	216	422	December 1988– April 1989	0–14	Distance (<50 m)	OR = 1.1, 95% CI: 0.5, 2.4	No measurements or calculated fields

Abbreviations: CI, confidence interval; HCC, high-current configuration; OR, odds ratio.
[a] The unit of analysis was dwelling.